Creating Copper Rotaxanes with Soft Nitrogen Based Kinetic Barriers

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The creation of synthetic molecular machines are within the scope of organic chemical techniques. Molecular motions move macrocycles, making motors, muscles, and machines.

Two interlocking components form the construct of the most basic molecular machines. The first component of rotaxanes is a long flexible dumbbell with two different binding sites and bulky stoppers at both ends. The second component of rotaxanes is a ring shaped component that can dock at either of the two sites (contingent on chemical conditions). An alternative rotaxane motif differs from the above design, with the ring component having two binding sites while the dumbbell has a single binding site. Catananes have two interlocking rings. The most common technique to achieve *switching* is accomplished photochemically,[1] electrochemically,[2,3] chemically,[4] or through the changing of the pH of the medium.[5] The requirement for a well-functioning system necessitates that the *switching* process be quantitative in order to preserve the molecular machine from destruction after a very small number of useful operations.

Many research groups have developed working molecular machines based on a variety of binding schemes. The most common include noncovalent interactions, such as π- π stacking[3,5] or hydrogen bonding[4]. Sauvage developed a *switching* system that relies upon the thermodynamic preference of copper(I) center to be 4-coordinate versus the preference of copper(II) center to be 5-coordinate.[2] Copper(I), which is bound to two phenanthrolines, is oxidized to copper(II), the system rearranges such that copper(II) can be bound to a phenanthroline and a terpyridine, making a 5-coordinate system. When copper(II) is reduced to copper(I), the system rearranges so that copper(I) can be bound,

once again, to the original two phenanthrolines, i.e., 4-coordinate system (figure 1). The rate of copper(I)-"4 coordinate" transitioning to copper(II)-"5-coordinate" is slow (k = 5 s^{-1} for rotaxanes).[6] The rate of transitioning from copper(II)-"5 coordinate" to copper(I)-"4-coordinate" is by contrast very fast (k > 500 s^{-1} for rotaxanes).[6]

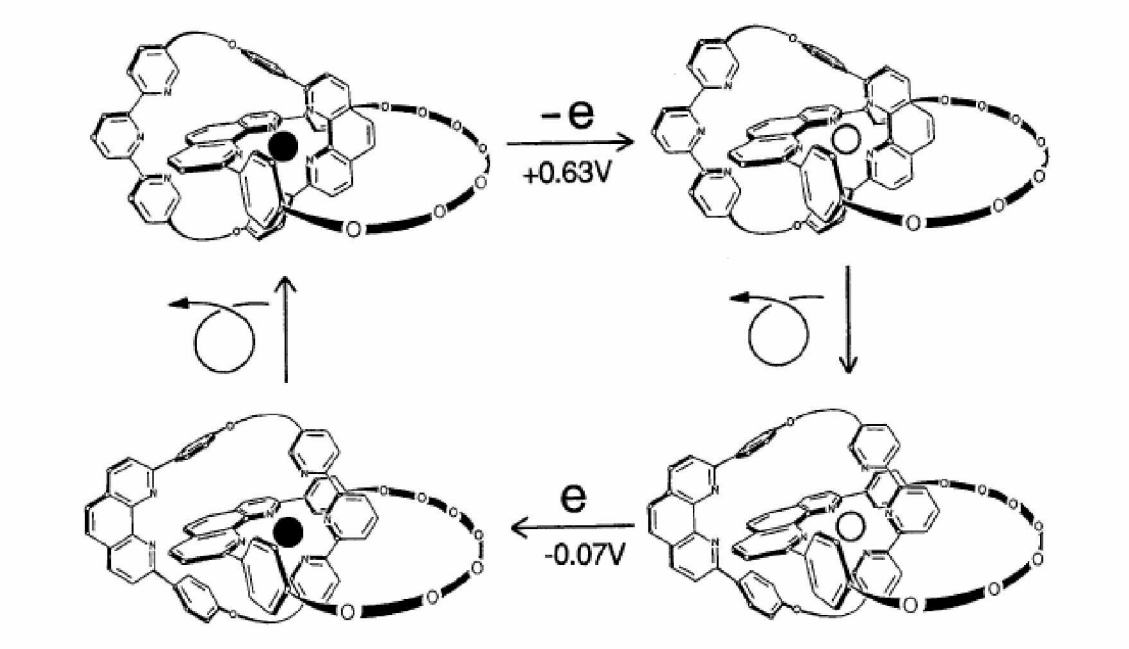
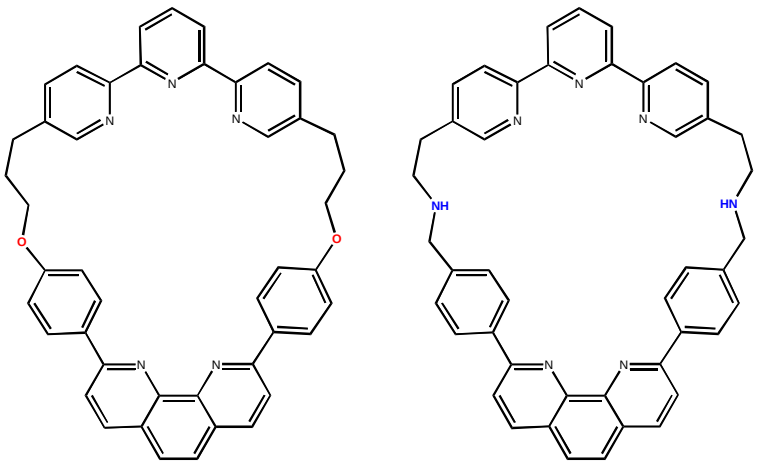


Figure 1: Switching scheme for Sauvage's catanane**.** The black dot is copper(1) and the white dot is copper(2). After oxidation of copper(1), the macrocycles switches from the 4 to the 5 cooridantion state. After reduction of copper(2) to copper(1), the macrocycle transitions from the 5 to the 4 coorinatation site.

Utilizing this information, we are proposing investigating an approach to bias the system by altering the kinetic barriers for the 4-to-5-coordinate transition, assuming that even slight changes to structure can have a large effects on the rate constant.

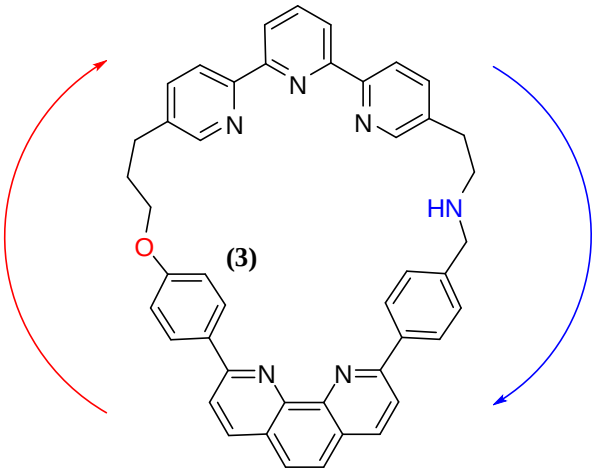
In the system being proposed, a secondary nitrogen linker will replace the ether oxygen within the macrocycle's chain of a rotaxane (figure 2).



(1) (2)

Figure 2: A side by diagram of Sauvage's catanane (with red oxygen linkers) and the proposed catanane (with blue amine linker).

The kinetics of the system will then be measured for the resulting rotaxane pirouetting electrochemically. If the nitrogen has any effect on the kinetics and the effect is different between the 4-to-5-coordinate switch and the 5-to-4-coordinate switch, then a unidirectional motor can be achieved by making a macrocycle where one spacer is an ether oxygen and the other side is a secondary amine. Since nitrogen is softer than oxygen, and copper(I) is softer than copper(II), there should be a preference for the copper(II) center to move in the direction of the oxygen linker during the 4-5 transition, and copper(I) to move towards the amine link in the 5-4 transition (Figure 3).



(3)

Copper(II)5 to Copper(I)4
Copper(I)4 to Copper(II)5

Even if the kinetics for bridging the oxygen are faster in both cases than that for passing the nitrogen, the system will still yield net unidirectional motion.[7]

Figure 3: Expected net movement of a phenanthroline macrocycle across the N-O ring.

If the nitrogen has no effect on kinetics, then derivative experiments can be attempted. The easiest includes the protonation of the alkyl amine, which has a pKa 4 units higher than pyridine. When the nitrogen is protonated, yielding a positive charge, it should repel the copper cation during the transition from the 4-to-5 and 5-to-4 coordinate systems. If kinetic rates are altered in the manner suggested in the prior paragraph, then a unidirectional system can be prepared. Kinetics can be measured at various pHs in order to ascertain the optimal difference in rates between these systems.

If the protonated nitrogen has no effect on kinetics, then the nitrogen can be alkylated to introduce steric barriers, which should provide a substantial effect in the catanane systems and modest effects on rotaxanes. The nitrogens can also be dialkylated to establish a permanent positive charge on the linker. Kinetic rates will be measured to see if there is an appropriate candidate for a unidirectional system. If the nitrogen is alkylated with two different groups, then the ring will be chiral, and if the dumbbell or macrocycle is made chiral by placing methyl groups on 3 and 3' positions on a bipyridine, it may interact to give a diasteriotopic transition state, which may be biased in one direction. Alkylation of the nitrogen with an alkyl group containing a terminal thiol can be implemented. The sulfur can then be annealed to a gold surface.

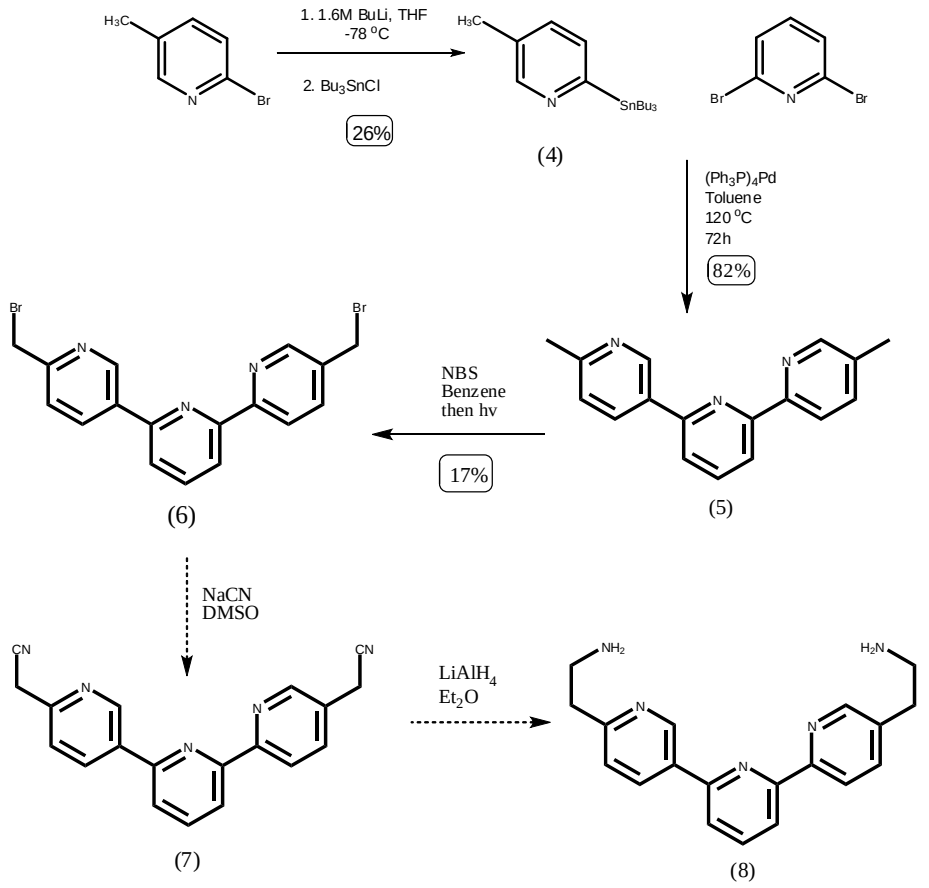
Synthesis of N-Macrocycles

Synthetic Scheme

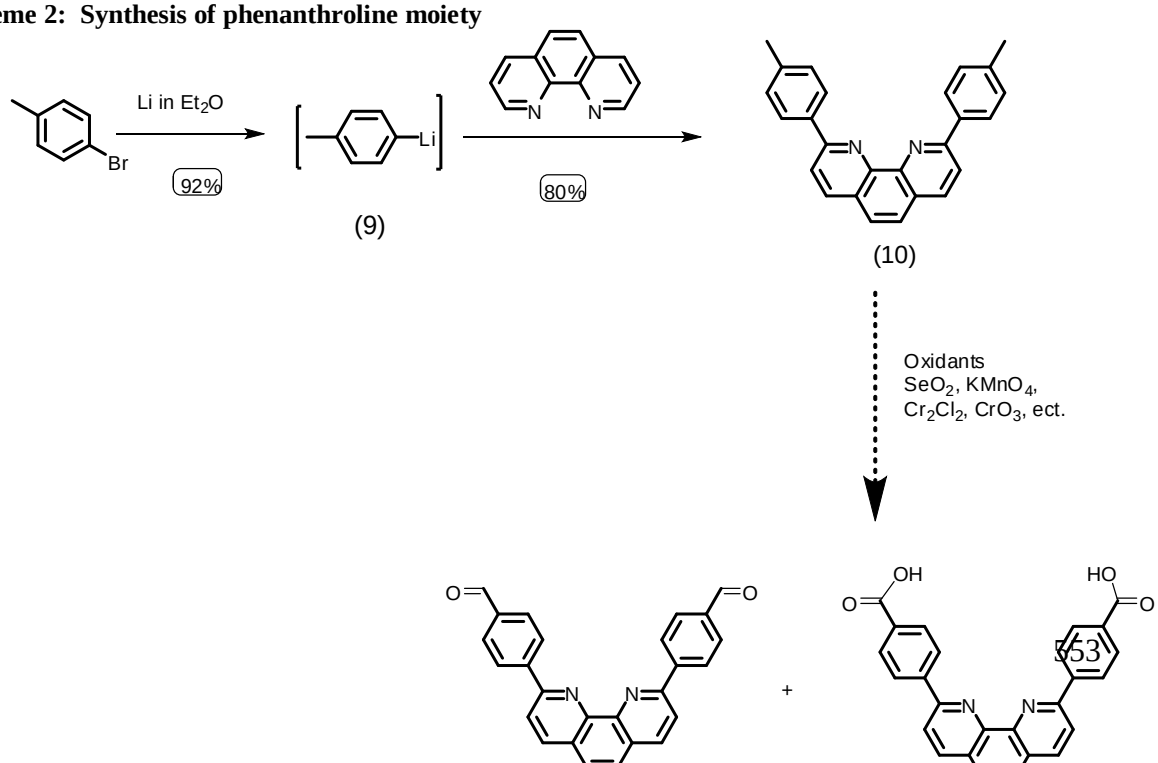
The synthesis will follow the plan in scheme 1, 2 and 3. The most challenging aspect of the macrocycle synthesis will be the macrocyclization step (Scheme 3). High dilution techniques will be used to help prevent the formation of larger macrocycles. No-D ^{1}H NMR[12] will be used to closely monitor the coupling step to determine the optimum condition for the reductive amination of phenanthroline **11** and terpyridine **8** so that the major product **2** contains one **11** and one **8** moeity. Synthesis of the amine bridged macrocycle is being performed in with two convergent synthesis of a terpyridine component **8** (scheme 1) and a phenanthroline moiety **11** (scheme 2), which will be coupled in a single macrocyclization step by reductive amination. Terpyridine **5** will be formed by the Stille coupling between two stannyl pyridines **4** and 2,6-dibromo pyridine. Both benzylic positions of **5** will be mono-bromonated using NBS and light to initiate a radical addition to form **6**. Sodium cyanide will perform an S_n2 reaction to replace the bromines with cyano groups giving **7**. The cyano groups will be reduced, forming the primary amine **8**.

The phenanthroline will be synthesized by addition of 4-lithio-toluene **9** to 1,10-phenanthroline to form **10**. The benzylic carbons will be oxidized to the aldehyde or carboxylic acid by standard allylic oxidation methods (CrO_4, SeO_2, etc.) yielding phenanthroline **11**.

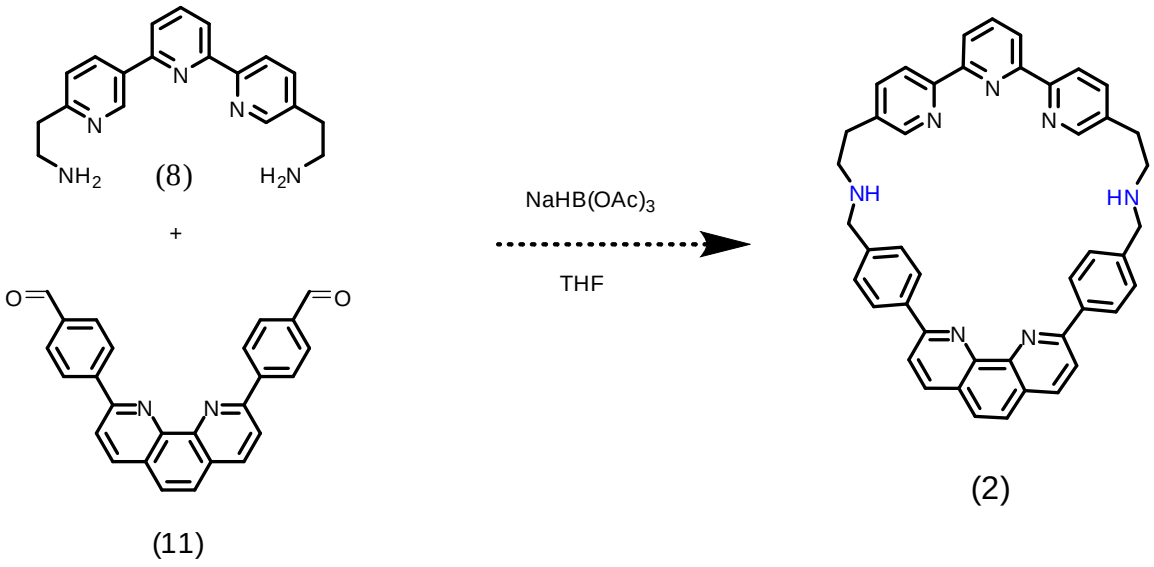
Scheme 1: Synthesis of terpyridine moiety



Scheme 2: Synthesis of phenanthroline moiety



Scheme 3: Macrocyclization of phenanthroline and terpyridine components



Completed Work

The portions of scheme 1 with a bold arrow indicate completed work. The dotted line corresponds to future plans. 5,5"-Dimethyl-2,2':6',2"-terpyridine (**5)** was made via a Stille coupling as described in the literature (scheme 1).[8] The Stille coupling of 2-tributylstanyl-5-methyl-pyridine (**4)** and 2,6-dibromopyridine was monitored using ^{1}H No-D NMR. Photochemical bromonation of (1) was preformed to generate 5,5'-Bis(bromomethyl)-2,2'-bipyridine (**5**) in low yeild.[13]

4-Lithiotolune (**9)** was prepared by metal halogen exchange of bromine for lithium in 4-bromotoluene. The lithium reagent was used to add 2 toluene molecules onto 1,10-phenanthroline.[11]

Non Dueterated ^{1}H NMR Spectroscopy of Stille coupling

In the Stille coupling of **4** and 2,6-dibromopyridine to form **5**, No-D ^{1}H NMR spectroscopy was used to monitor the progress of the reported 5 day reaction at 120 °C. The results showed that the reaction was 90% complete after 2 days at 80 °C. During the reaction, No-D ^{1}H NMR spectra were taken, and integrations were found for peaks A-R (figure 4, 5, 6).

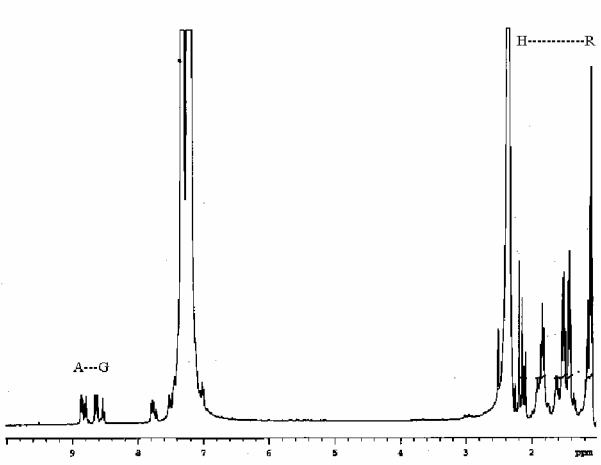


Figure 4: ^{1}H No-D spectra taken after 1.5 days.

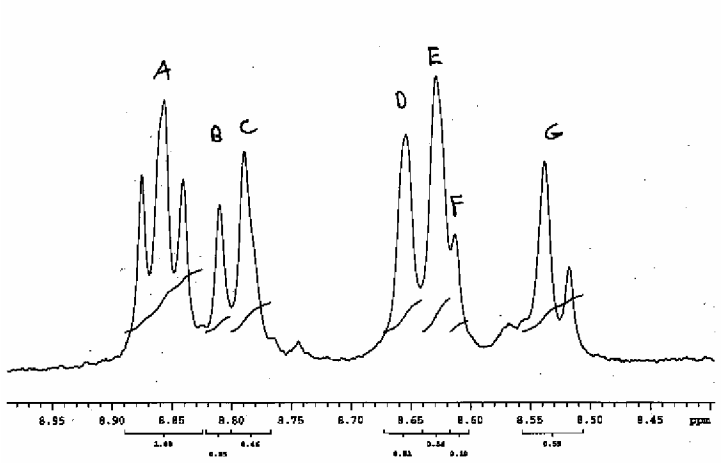


Figure 5: ^{1}H No-D spectra of the aromatic region illustrating peak assignments.

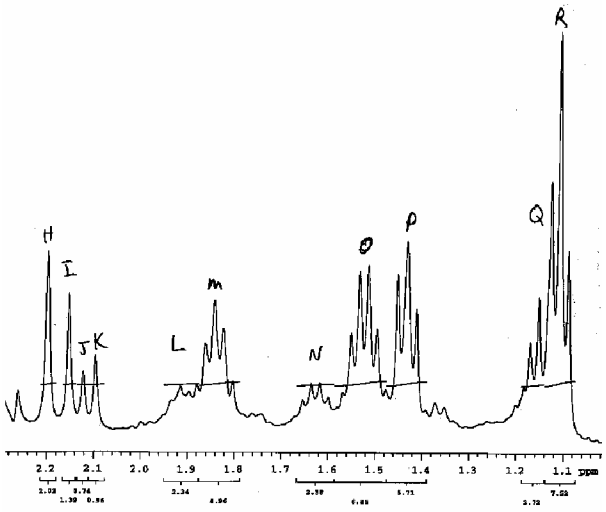


Figure 6: ^{1}H No-D spectra of the aliphatic region illustrating peak assignments.

The aromatic peaks 8-9 ppm were normalized by dividing each peak integration by the total integration value for all peaks from 8.5-9.0 ppm. The relative intensities were graphed vs. time (figure 7). A similar process was done for the alkane peaks from 0.5-2.3 ppm (figure 8).

Over the course of the reaction, 5 chemicals were observed: the two starting materials, two products, and an intermediate that was not isolated. The starting material peaks slowly decreased through the course of the reaction. The peaks from the

intermediate increased rapidly for 8 hours, and then slowly decreased. The product peaks increased slowly. Peak C corresponds to the first starting materials. Peaks L, N, and Q relate to the tributylstannyl **4** starting material. Peaks A, B, D and E arise from the first product **5**. Peaks M, O, and R come from the second product. Peaks G and F are from the intermediate. Other peaks were hidden by the solvent. The reaction did not proceed through clear first or second order kinetics, which is not uncommon of catalytic reactions.

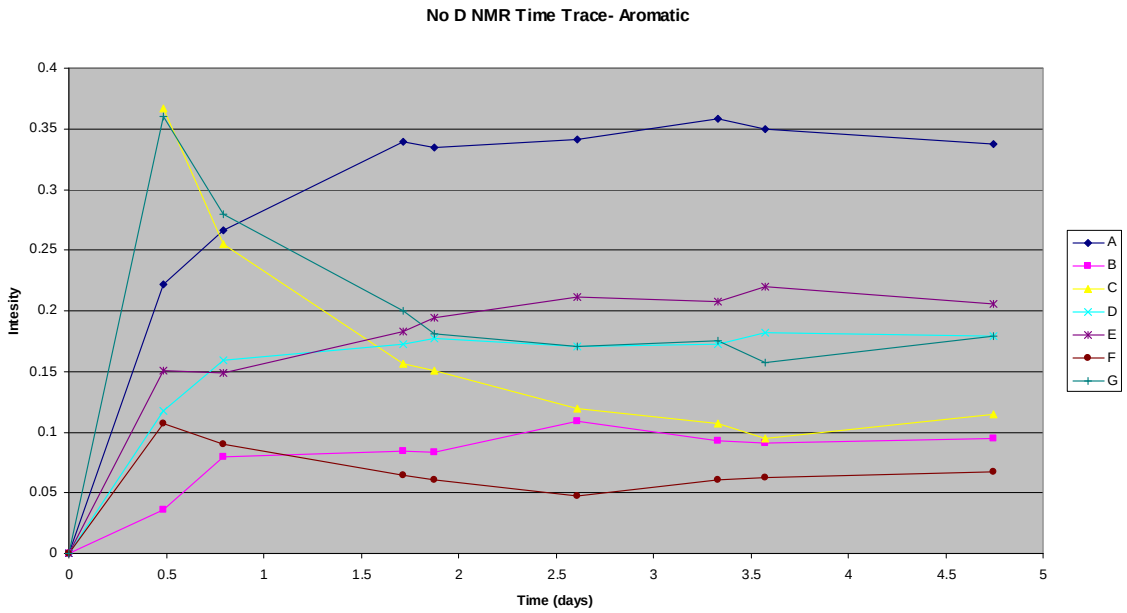


Figure 7: No-D NMR graph of time vs. relative concentration for the aromatic region.

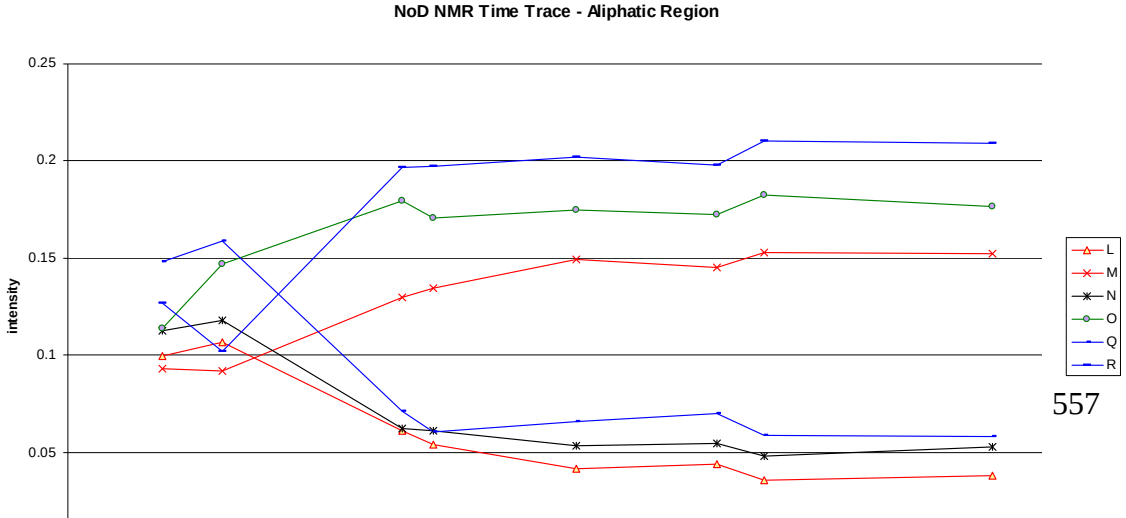


Figure 8: No-D NMR graph of time vs. relative concentration for the aliphatic region

Future Work

The synthesis of the macrocycle will be completed as previously described. The rotaxane will be made by using the threading followed by stoppering approach,[2] using the previously constructed N-hinged macrocycle.

Kinetics of the rotaxane switching can be monitored by electrochemical techniques as well as UV/Vis spectroscopy.[2] Further experiments to probe the kinetic barrier of the transition will be designed and performed. The characterized catanane or rotaxane will be annealed to a gold surface, and its chemistry will be explored with electrochemistry and Raman spectroscopy.

Synthesis and characterization of the N-O catanane **3** will be carried out if the rates of 4-5 or 5-4 coordinate transition the N-N catanane **2** differs from the rates of the corresponding O-O catanane **1**.

Conclusion

In this paper, the general methods for creating unidirectional motion in a catanane were proposed. Future research endeavors will determine the abilities of the proposed

molecular machine. Following the coupling reaction with NMR will allow for precise tailoring of conditions to get the fitting macrocycle.

While there have yet to be real world applications of synthetic molecular machines, biological systems have been utilizing chemical motors for activities ranging from movement of muscles to transport of organelles during cell division. If biology gives any clue as to these new molecules application, likely, it will be in the field of moving small molecules precisely or more efficient macroscopic transport.

Copper based catananes move a bit too slow to be useful for logic gates, but the large binding energies make them ideal for stable memory devices, orders of magnitude smaller than anything available today. While lithography techniques are only adaptable to building 2D devices, synthetic chemists are adept at making 3D molecular architectures. This allows for the design of three dimensional circuits that can utilize space far more efficiently. Finally, because molecular machines are synthesized via standard chemistry techniques, they are amenable to being scaled up to create very cheap machines.

Experimental

General

Nuclear Magnetic Resonace Spectra were taken with the Varian VXR 400 spectrometer. Starting materials were purchased from Acros Organics, and used without further purification. Dry solvents were purified using a Pure Solv 400-6-MD solvent system. All compounds synthesized have been previously reported.

5-Methyl-2-tributylstannyl pyridine (4)

2-Bromo-5-methyl pyridine (5 g, 0.0291 mol) was dissolved in THF (100 mL) in flame dried glassware and then degassed with N_2. The solution was cooled down to – 78 °C. 1.6 M *n*-BuLi in hexane (22.5 mL) was added portionwise to the THF solution so its temperature did not exceed –60 °C. The solution turned dark orange. The reaction was stirred for 90 min, and the reaction mixture turned black. Tributylstannyl chloride (12 mL) was added to the reaction mixture portionwise over 30 minutes. The reaction was kept at – 78 °C for 2 h, and then allowed to slowly warm up to RT. After 12 h of stirring at RT, the mixture turned orange. The orange liquid was washed with H_2O, and the aqueous portions were extracted with Et_2O. The solvent was removed *in vacuo* leaving a yellow oil. The mixture was purified via vacuum distillation to yield 10.78 g (95%) of **4**. Bp 100 °C/15 mTorr.

^{1}H NMR ($CDCl_3$): δ = 8.61 (1 H, s), 7.32 (2 H, m), 2.31 (3 H, s), 1.56 (6 H, p), 1.34 (6 H, tq *J* =7.25Hz), 1.12 (6 H, t, *J* = 8.14 Hz), 0.89 (9 H, t, *J* = 7.3 Hz)

5,5''-Dimethyl-2-2':6'2''-terpyridine (5)

5-Methyl-2-tributyl-stannyl pyridine (**4**) (1.04 g, 4.36 mmol), 2,6-dibromopyridine (5 g, 0.0131 mol), and tetrakis(triphenylphosphine) palladium (0.403 g, 0.349 mmol) were dissolved in toluene (33 mL). The mixture was stirred at 120 °C for 3 days. The mixture turned black after 1 day. After 3 days, the solution was poured into 5 M HCl. The aqueous layer was washed with CH_2Cl_2, and the organic layers were extracted with 5 M HCl. The aqueous layer was adjusted to pH 9 with NaOH and Et_3N, turning the solution pink. The aqueous layer was extracted with a mixture of Et_3N (5%) and CH_2Cl_2 (95%).

The solvent was removed *in vacuo*. The solid was recrystalized with hot EtOAc yielding 0.93 g (82%) of **5** as white needles.

^{1}H NMR ($CDCl_3$): δ = 8.53 (2H s), 8.51 (2 H d, *J* = 8.42 Hz), 8.39 (2 H d, *J* = 7.87 Hz), 7.92 (1 H, t, *J* = 7.87 Hz), 7.66, (2 H, dd, *J* = 7.87, 1.64 Hz), 2.39 (3 H, s)

5,5'-Bis(bromomethyl)-2,2'-bipyridine (6)

5,5"-Dimethyl-2-2':6'2"-terpyridine (**5**) (0.0217 g, 0.831 mmol) and N-Bromo-Succinimide (0.074 g, 0.4 mmol) were dissolved in benzene (2.2 mL) and refluxed for 30 min. The solution turned yellow. The flask was removed from the heating bath, and then it was irradiated with a 150 W bulb for 2 h. A white precipitate appeared. The solvent was removed *in vacuo*, and then the solid was dissolved in CH_2Cl_2. The organic layer was washed with H_2O, and then 2 M Na_2SO_3 in H_2O. The aqueous layers were extracted with CH_2Cl_2. The solvent was removed *in vacuo*. The orange impurity was removed by gently rinsing the solid with acetone (.0061 g, 0.0014 mmol, 17%).

^{1}H NMR ($CDCl_3$): δ = 8.70 (2 H, s), 8.58 (2 H, d, *J* = 8.24 Hz), 8.45 (2 H, d, *J* = 7.87 Hz), 7.96 (1 H, t, *J* = 7.69 Hz), 7.89 (2 H, dd, *J* = 8.23, 2.38 Hz), 4.56 (4 H, s)

4-Lithiotoluene (9)

Lithium (0.58 g, 0.084 mol) was washed with toluene, and added to dry ether (25 mL) that was degassed with argon. A small portion of 4-bromotoluene (0.3 mL) was added to the mixture. The flask was warmed with a heat gun until the ether began refluxing.

Additional 4-bromotoluene (2.8 mL) was added portionwise over 15 minutes. The solution changed color from yellow to orange to brown after successive additions of 4-bromotoluene. After an additional 15 minutes, the mixture stopped refluxing. The solution was canulated into a dry rb flask under argon, to remove the solid impurities. The concentration of the organolithium solution was determined utilizing No-D ^{1}H NMR spectroscopy employing 1,4-cyclooctadiene (0.998 g) as a titer. The final concentration was determined to be 0.0231 mol 4-litiotoluene (92%) in 19 mL dry ether. This solution was used 1 h later in the following reaction.

^{1}H NMR (Et_2O): δ = 7.83, (2 H, d, J = 7.33 Hz), 6.83 (2 H, d, *J* = 7.14 Hz), 2.22 (3H, s)

2,9-Di(p-tolyl)-1,10-phenanthroline (10)

1,10-Phenathroline (0.99 g, 5.49 mmol) was partially dissolved in dry toluene (12 mL). The suspension was degassed with argon, and then cooled to 0 °C. 1.21 M **9** (19mL, 0.0231 mol) solution in ether was added to the phenanthroline suspension dropwise over 30 min. The solution first turned opaque bright yellow, and then dark red. The solution was stirred at 20 °C for 24 h, and then cooled to 0 °C. H_2O (2 mL) was added over 10 min to the solution. Additional H_2O (18mL) was added over 10 minutes. The solution turned translucent yellow. The organic layer was washed with H_2O, and the aqueous layer was extracted with CH_2Cl_2. MnO_2 (45 g) was added to the solution in 5 g portions over 3 days (30 g on the first day, and 5 g on each successive day). The mixture was dried with $MgSO_4$. The MnO_2 and $MgSO_4$ filtered over a fine sintered disk funnel giving an orange liquid. The solvent was removed *in vacuo* leaving **10** as a orange solid (80%).

^{1}H NMR ($CDCl_3$): δ = 8.39, (4 H, d, *J* = 8.21 Hz), 8.29 (2 H, d, *J* = 8.40 Hz), 8.13, (2 H, d, *J* = 8.40 Hz), 7.77 (2 H, s), 7.40 (4 H, d, *J* = 8.01 Hz), 2.48 (6 H, s)

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